Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19

Huiqing Li,[1,2&] Shenghua Tian,[1,2&] Ting Chen,[1,2&] Zhenhai Cui,[1,2] Ningjie Shi,[1,2] Xueyu Zhong,[1,2] Kangli Qiu,[1,2] Jiaoyue Zhang,[1,2] Tianshu Zeng,[1,2] Lulu Chen,[1,2] Juan Zheng[1,2]

[1] Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;

[2] Hubei provincial Clinical Research Center for Diabetes and Metabolic Disorders, Wuhan, China;

& These authors contributed equally to this work and are considered as co-first authors.

Corresponding authors: Dr. Juan Zheng, Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, zhengjuan25@163.com

and

Dr. Lulu Chen, Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, cheria_chen@126.com

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Abstract

Context

No studies evaluated the prospective association between hyperglycemia assessed by laboratory measurements and the risk of mortality among patients with coronavirus disease 2019 (COVID-19).

OBJECTIVE

We aimed to evaluate the association between different degrees of hyperglycemia and the risk of all-cause mortality among hospitalized patients with COVID-19.

DESIGN

A retrospective study.

SETTING

Union Hospital in Wuhan, China.

PARTICIPANTS

453 patients were admitted to the hospital with laboratory-confirmed SARS-Cov-2 infection from 22 January 2020 to 17 March 2020.

MAIN OUTCOMES AND MEASURES

Patients were classified into four categories: normal glucose, hyperglycemia (fasting glucose

5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%), newly diagnosed diabetes (fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%), and known diabetes. The major outcomes included in-hospital mortality, intensive care unit (ICU) admission, and invasive mechanical ventilation (IMV).

RESULTS

Patients with newly diagnosed diabetes had the highest percentage to be admitted to the ICU (11.7%) and require IMV (11.7%), followed by patients with known diabetes (4.1%; 9.2%) and patients with hyperglycemia (6.2%; 4.7%), compared with patients with normal glucose (1.5%; 2.3%), respectively. The multivariable-adjusted hazard ratios of mortality among COVID-19 patients with normal glucose, hyperglycemia, newly diagnosed diabetes, and known diabetes were 1.00, 3.29 (95% confidence interval [CI] 0.65-16.6), 9.42 (95% CI 2.18-40.7), and 4.63 (95% CI 1.02-21.0), respectively.

CONCLUSION

We firstly showed that COVID-19 patients with newly diagnosed diabetes had the highest risk of all-cause mortality compared with COVID-19 patients with known diabetes, hyperglycemia and normal glucose. Patients with COVID-19 need to be under surveillance for blood glucose screening.

Introduction

The ongoing outbreak of COVID-19 is rapidly escalating worldwide. The new virus that caused this epidemic was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has now become a global catastrophe. As of Apri1 30, 2020, about 3.1 million cases have been confirmed and about 220,000 deaths were caused by COVID-19 around the world.[1] Recent data suggest that most people with COVID-19 have common comorbidities including diabetes, cardiovascular disease, and hypertension.[2]

Diabetes is one of the leading causes of morbidity, which results in huge health and financial burden worldwide.[3] Diabetes is a primary risk factor for the development of severe pneumonia

and a septic course due to virus infections and occurs in around 20% of patients with severe pneumonia. [4, 5] Hyperglycemia and a history of type 2 diabetes are independent predictors of mortality and morbidity in patients with SARS.[6] Diabetes is also identified as a major contributor to disease severity and mortality in the Middle East Respiratory Syndrome (MERS-CoV).[7] Several studies have shown that COVID-19 is associated with hyperglycemia particularly in the elderly with type 2 diabetes.[8] Two recent studies have found that 10.1% or 7.4% COVID-19 patients reported a history of diabetes.[9, 10] Two other studies suggest that the risk for death from COVID-19 is up to 50% higher in people with a history of diabetes than in those without.[11, 12] However, no studies have evaluated the prospective association between hyperglycemia assessed by laboratory measurements and the risk of mortality among patients with COVID-19. The first aim of the present study was to investigate the clinical characteristics, laboratory findings, treatments, and major outcomes among hospitalized COVID-19 patients with different degrees of hyperglycemia. The second aim was to assess the association between different degrees of hyperglycemia and the risk of all-cause mortality among hospitalized patients with COVID-19.

Methods

Study design and participants

This retrospective observational study included adult patients who were diagnosed with 2019-

nCoV pneumonia and hospitalized in Wuhan Union Hospital between January 22, 2020 and March 17, 2020. A diagnosis of COVID-19 illness was based on a positive SARS-CoV-2 laboratory result under the World Health Organization interim guidance.[13] Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology was designated by the government to undertake the treatment of severe COVID-19 patients. Until April 10, 2020, 453 inpatients were included in the present analysis, of whom 39 were fatal and 414 recovered. This study was conducted according to the ethics committee of Tongji Medical College of Huazhong University of Science and Technology. Informed consent was replaced by oral consent. The retrospective study used anonymous clinical data for analysis.

Data collection

The epidemiological data, clinical information, laboratory and radiological characteristics, chest computed tomography (CT) scan, treatment and outcome data of patients (recovery, death or transfer to other hospitals) were collected by a standardized electronic medical record data collection form. A well-trained team of doctors and researchers from Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology independently input and cross-checked the data into a computer database. Two researchers (T.S., C.Z) in our team independently reviewed clinical data of all laboratory-confirmed patients infected with SARS-CoV-2. We contacted the clinician in charge of the patient's care

for the missing data that needed to be supplemented. Since some patients could not cooperate with medical history collection when they were admitted to the hospital, we obtained their medical history and information before admission by contacting their close relatives and consulting the medical records of previous hospital visits. Under government policies, some discharged patients were followed up and recorded. Patients with incomplete information, especially those without clinical results, or those diagnosed with pneumonia by other known pathogens, were excluded.

Basic information (age, sex, smoking, and shared medical history) and epidemiological exposure history were collected for each patient (addendum). A history of exposure was defined as exposure to a confirmed SARS-CoV-2 infection or to the Wuhan Huanan seafood market. Clinical manifestations (fever, fatigue, cough, myalgia, red eyes, dyspnea, headache, rhinorrhea, chest pain, diarrhea, nausea and vomiting, palpitations, loss of appetite, dyspnea, etc.) with the changes from onset to discharge were recorded. Vital signs (heart rate, respiratory rate, and blood pressure) were measured and recorded at admission, and height and weight were self-reported. Within 3 days after admission to the hospital, laboratory results including standard blood count (absolute white blood cells and lymphocytes, hemoglobin concentration, platelet count, arterial blood gas analysis, supply, oxygen partial pressure [PaO2]), blood biochemistry (including kidney and liver, creatine kinase, fasting plasma glucose, HbA1c,

lactate dehydrogenase and the electrolyte), coagulation, procalcitonin, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), myocardial enzyme spectrum and normal bacteria, fungi and viruses, were input before the steroid therapy. Other data included medical imaging, treatment regimens (antiviral and antimicrobial agents, systemic corticosteroids, immunoglobulin G, respiratory support [such as nasal tubes, high-flow nasal intubation, noninvasive and invasive mechanical ventilation]), and prognosis (discharge or death). Recovered patients without any obvious symptoms and signs, having the lesions absorbed more than before by chest CT scan, and with repeated negative results of SARS-Cov-2 virus nucleic acid tests, were discharged from the hospital.

Classification of glucose abnormality

Patients were classified into four categories based on the first laboratory measurement and a history of diabetes after hospital admission: normal glucose, hyperglycemia (fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%), newly diagnosed diabetes (fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%), and known diabetes.

Study outcomes

The main composite endpoints were invasive mechanical ventilation (IMV), admission to the intensive care unit (ICU), or death. The duration of follow-up for each patient (person-days)

was calculated from the first confirmed date of COVID-19 to the index date of discharge, death of inpatients, or transfer to other hospitals. We also included other outcomes in the analyses. The definitions of sars-cov-2-associated acute respiratory distress syndrome (ARDS) and shock referred to the interim guidance of WHO for SARS-CoV-2[13]. Acute cardiac injury was defined as elevated serum levels of cardiac biomarkers (such as CK-MB and hypersensitive cardiac troponin I) above the 99th percentile reference limit, or new abnormalities found in the electrocardiogram and echocardiography.[14] Acute kidney injury was diagnosed according to KDIGO clinical practice guidelines.[15] According to the Chinese COVID-19 management guidelines (version 6.0), the severity of COVID-19 was divided into three levels: mild, severe and critical. Clotting disease was diagnosed if prothrombin time (PT) prolonged over 3 seconds or activation of partial thromboplastin time (APTT) prolonged over 5 seconds.[16] Hypoproteinemia was defined as blood albumin less than 30g/L.

Statistical analysis

Differences in demographic, history of diseases, clinical symptoms, laboratory measurements, treatment and clinical outcomes among patients with different glucose status (normal glucose, hyperglycemia, newly diagnosed diabetes, and known diabetes) were assessed using Pearson's chi-square or the Fisher's exact test for categorical variables and the General Linear Model for continuous variables after adjustment for age and sex. Cox proportional hazards regression was

used to estimate hazard ratios (HRs) for all-cause mortality among patients with different glucose status. Four models were used: Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, smoking, systolic blood pressure, and total cholesterol; Model 3 adjusted for variables in Model 2 as well as using IMV, admission to the ICU, using antihypertensive medications, and using lipid-lowering agents; Model 4 adjusted for variables in Model 3 as well as using glucose-lowering drugs before hospital admission and during hospitalization, and using corticosteroid. We used the restricted cubic spline nested in time-dependent Cox models to test whether there was a dose-response or nonlinear association of fasting glucose as a continuous variable with the all-cause mortality risk. All the statistical analyses were performed with SPSS statistics V.25.0 for Windows software package (IBM) and SAS for Windows version 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided $p<0.05$ was considered statistically significant.

Patient and public involvement

This was a retrospective study and no patients were involved in the study design, setting the research questions, or the outcome measures directly. No patients were asked to advise on interpretation or writing up of the results.

Results

Until March 17, 2020, clinical data were collected from 453 patients with laboratory-confirmed

SARS-Cov-2 infection. As of April 10, 2020, all hospitalized patients had outcomes. Of them 114 patients were mild, 233 patients were severe and 106 patients were critical according to the clinical classification. General characteristics of the study population at baseline are given in Table 1. The median age of patients was 61 (interquartile range 49-68) years. Patients who had known diabetes, newly diagnosed diabetes, and hyperglycemia were slightly older, their baseline body mass index was higher, and they were more often past or current smokers and had more histories of hypertension and stroke as compared with those with normal glucose.

The laboratory parameters among COVID-19 patients are presented in Table 2. Patients with newly diagnosed diabetes had the highest and patients with known diabetes had higher mean values of CRP, white blood cell count, erythrocyte sedimentation rate, fibrinogen, lactate dehydrogenase, blood urea nitrogen and fasting glucose than patients with either normal glucose or hyperglycemia.

Table 3 shows the treatments and outcomes among COVID-19 patients with different glucose status. Patients with newly diagnosed diabetes were more likely to be admitted to the ICU (11.7%) and require IMV (11.7%), followed by patients with known diabetes (4.1%; 9.2%) and patients with hyperglycemia (6.2%; 4.7%), compared with patients with normal glucose (1.5%; 2.3%), respectively. Patients with known diabetes and newly diagnosed diabetes had higher

COVID-related complications including ARDS (3.1-10.5% vs 0.8-3.1%), acute kidney injury (15.3-17.0% vs 1.5-3.1%), shock (11.2-23.4% vs 2.3-4.7%), and hypoalbuminemia (36.7-39.4% vs 10.8-19.4%), as well as higher severe or critical types of COVID-19 (82.7-89.4% vs 61.4-72.1%) compared with patients with normal glucose or hyperglycemia. Patients with known diabetes and newly diagnosed diabetes were more likely to use antihypertensive drugs, glucose-lowering medicines during hospital admission, lipid-lowering agents, corticosteroid treatment, oxygen support, and stay longer at hospital compared with patients with normal glucose or slight hyperglycemia.

During a mean follow- up period of 29.5 days (range 1-70 days), 39 inpatients died. The results for the multivariate-adjusted Cox models for all-cause mortality in different glucose categories are shown in Table 4 and Figure 1. Relative to normal glucose, all-cause mortality increased in hyperglycemia (HR 3.29; 95% confidence interval [CI] 0.65-16.6), newly diagnosed diabetes (HR 9.42; 95% CI 2.18-40.7), and known diabetes (HR 4.63; 95% CI 1.02-21.0), after adjusting for age, sex, smoking, systolic blood pressure and total cholesterol (Model 2). After further adjustment for using antihypertensive drugs, using lipid-lowering agents, admission to ICU, and using IMV (Model 3), these associations did not change; however HR of mortality for known diabetes became higher than that for newly diagnosed diabetes after additional adjustment for using glucose-lowering drugs before hospital admission and during

hospitalization, and using corticosteroid (Model 4).

When fasting glucose was considered as a continuous variable by using restricted cubic splines, a graded positive association of fasting glucose with all-cause mortality was observed among COVID-19 patients after excluding known diabetes (Figure 2).

To assess the potential hyperglycemia to exposed COVID-19, we performed one sensitivity analysis among patients with newly diagnosed diabetes based on the first laboratory measurement of fasting glucose and HbA1c after hospital admission. Multivariable-adjusted (Model 2) HRs of mortality were 3.30 (95% CI 0.65-16.6) among patients with hyperglycemia, 9.06 (95% CI 1.88-43.6) among patients with fasting glucose ≥7 mmol/L only but no HbA1c measurements, 10.4 (95% CI 1.97-54.7) among patients with fasting glucose ≥7 mmol/L and HbA1c <6.5%, 9.23 (95% CI 1.87-45.5) among patients with fasting glucose ≥7 mmol/L and HbA1c ≥6.5%, and 4.62 (95% CI 1.02-20.9) among patients with known diabetes, compared with patients with normal glucose (online Table 1).

Discussion

Our study found that newly diagnosed diabetes at the first measurement of hospital admission and a history of diabetes were associated with an increased risk of all-cause mortality in

hospitalized patients with COVID-19. Moreover, the present study was the first one to show that COVID-19 patients with newly diagnosed diabetes based on the first laboratory measurement after hospital admission had the highest risk of mortality compared with COVID-19 patients with known diabetes, hyperglycemia and normal glucose, and this association was independent of major cardiovascular risk factors.

Several earlier studies have shown a link between a history of diabetes and COVID-19. Two studies in Wuhan indicated that 20% of 41 laboratory-confirmed COVID-19 patients (median age of 49 years)[17] and 10.1% of 138 laboratory-confirmed COVID-19 patients (median age of 56 years)[9] had a history of diabetes. According to the Chinese National Diabetes Survey in 2017, the prevalence of diabetes among people over 20 years old was 12.8% (6.0% of known diabetes and 6.8% of asymptomatic/newly diagnosed diabetes), and the prevalence of diabetes among people of 60-69 years old was 28.8% (14.9% of known diabetes and 13.9% of newly diagnosed diabetes).[18] The present study indicated that 21.6% of hospitalized COVID-19 patients reported a history of diabetes, 20.8% of COVID-19 patients were newly diagnosed as diabetes (fasting glucose ≥7.0 mmol/L and/or HbA1c ≥6.5%), and 28.4% of COVID-19 patients were diagnosed as hyperglycemia (fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%) at the first measurement of hospital admission, substantially higher compared with previous studies. Several possible reasons for the higher prevalence of known diabetes and

newly diagnosed diabetes in the present study might be considered: (1) All study samples were older with a median age of 61 years. (2) All hospitalized patients were laboratory-confirmed COVID-19, and were at a state of stress as hypoxia and inflammation, resulting in a significant rise in blood glucose. Our study also showed that patients with newly diagnosed diabetes and hyperglycemia had more often fever, cough, and dyspnea as well as higher levels of inflammatory indicators such as CRP, erythrocyte sedimentation rate and white blood cell count. (3) COVID-19 infection reduces angiotensin-converting enzyme 2 (ACE2) expression, which induced cellular damage, hyperinflammation, and respiratory failure.[19] The expression of ACE2 on pancreatic β-cells can lead to a direct effect on β-cell function.[20-22] Although these findings have not been verified in humans, they suggest that diabetes might be a risk factor for a severe form of COVID-19 disease and this infection could induce new-onset diabetes. [20-22] Acute kidney injury and abnormal liver function were higher in the present study especially in patients with newly diagnosed diabetes. The damage to key organs of glucose metabolism (liver and kidney) can lead to a significant effect on blood glucose.[23-25] The use of drugs, especially corticosteroids, can raise blood glucose. We found that the percentage of using corticosteroid was the highest among the patients with newly diagnosed diabetes, followed by patients with known diabetes and hyperglycemia, compared with patients with normal blood glucose.

Population-based cohort studies have found that people with either a history of diabetes or

asymptomatic diabetes had a higher risk of mortality than people with normal glucose.[26] However, very few studies have compared the mortality rate between COVID-19 patients with and without a history of diabetes or hyperglycemia. One Chinese case-control study indicated that mortality rates were 35.4% and 20.3% among COVID-19 patients with and without a history of diabetes, respectively.[27] Another US study found that COVID-19 patients with a history of diabetes and/or uncontrolled hyperglycemia had a markedly higher mortality than patients without diabetes (28.8% vs 6.2%).[28] However, no previous studies have assessed the association between different glucose status based on the American Diabetes Association's criteria and mortality, and no studies have controlled potential confounding factors in assessing the above association. The present study demonstrated that hospitalized COVID-19 patients with newly diagnosed diabetes at the first measurement of hospital admission were more likely to be admitted to the ICU and require IMV, had the highest prevalence of COVID-19-related complications including ARDS, acute kidney injury, shock and hypoalbuminemia, and also had the longest hospital stay, followed by patients with known diabetes and patients with hyperglycemia, compared with patients with normal glucose. Moreover, we firstly showed that COVID-19 patients with newly diagnosed diabetes at the first measurement of hospital admission had the highest risk of mortality compared with COVID-19 patients with known diabetes, hyperglycemia and normal glucose, although we also found that COVID-19 patients with known diabetes had an increased risk of mortality compared with patients with normal

glucose. These results were independent of major cardiovascular risk factors including age, sex, smoking, blood pressure, blood total cholesterol, using antihypertensive drugs, using lipid-lowering agents, admission to ICU, and using invasive mechanical ventilation. However, the relative risk of mortality among patients with known diabetes became higher than in those with newly diagnosed diabetes after adjustment for using glucose-lowering drugs before hospital admission and during hospitalization, and using corticosteroid. This can be speculated that COVID-19 patients with known diabetes using glucose-lowering drugs to control blood sugar might have a protective effect on the death risk.

Since COVID-19 patients with newly diagnosed diabetes after hospital admission might include patients with a significant rise in blood glucose due to stress as hypoxia and inflammation after COVID-19 and patients with asymptomatic diabetes after COVID-19, we further compared the relative risk of mortality among patients with newly diagnosed hyperglycemia up to diabetes (fasting glucose ≥7.0 mmol/L and HbA1c <6.5%) versus patients with asymptomatic diabetes (fasting glucose ≥7.0 mmol/L and HbA1c ≥6.5%). Patients with hyperglycemia up to diabetes and patients with asymptomatic diabetes contributed equally to the all-cause mortality risk, and both had a higher risk of mortality than patients with known diabetes as compared with patients with normal glucose (Online Table 1). These results suggest that the risk of disease severity and poor prognosis of COVID-19 including mortality

significantly increases with newly diagnosed diabetes after hospital admission. Thus COVID-19 patients need to be under surveillance for blood glucose screening and COVID-19 patients with newly diagnosed diabetes should be paid more attention to the combination therapy for all COVID-19-related complications.

There are some mechanisms that newly diagnosed diabetes and/or known diabetes might play a role in COVID-19 infection and poor prognosis. Hyperglycemia and a history of diabetes are independent predictors of mortality and morbidity in patients with SARS.[6] It could be that these patients have a state of metabolic inflammation that predisposes them to an enhanced release of cytokines. For COVID-19, a cytokine storm that showed greatly elevated levels of inflammatory cytokines has been implicated in the multi-organ failure in patients with severe diseases.[29] Metabolic inflammation caused by hyperglycemia can also damage the immune system, reducing the body's ability to cope with infection, impairing the healing process and prolonging recovery time. An animal model shows that the complication of type 2 diabetes causes an immune disorder and enhances disease severity following MERS-CoV infection.[30]On the other hand, ACE2 has been confirmed as the receptor for the coronavirus spike protein. ACE2 has protective effects primarily regarding inflammation. COVID-19 infection reduces ACE2 expression, which induces cellular damage, hyperinflammation, and respiratory failure.[19] Acute hyperglycemia has been shown to upregulate ACE2 expression on

cells that might facilitate viral cell entry, while chronic hyperglycemia is known to downregulate ACE2 expression making the cells vulnerable to the inflammatory and damaging effect of the virus.[12] This may be one reason why patients with newly diagnosed diabetes have a worse prognosis than those with known diabetes.

This study is the first retrospective study to assess the different hyperglycemia status assessed by laboratory measurements with the risk of mortality among patients with laboratory-confirmed COVID-19. The relatively rich clinical data and numerous events also strengthen the results. There are some limitations to this study. First, our analyses adjusted for some confounding factors, however, unmeasured factors, such as body mass index, beta cell autoantibodies, could not be evaluated because there was relatively insufficient maintenance in an early stage of the epidemic outbreak and most sickest patients or patients who died during hospitalization did not measure height and weight. Second, not all patients had HbA1c tests, which may have some impacts on the accuracy of our blood glucose grouping. Third, using fasting glucose ≥7.0 mmol/L and HbA1c ≥6.5% as cutpoints to newly diagnose diabetes might have a potential misclassification bias because a significant rise in blood glucose for stress as hypoxia and inflammation was found among patients after COVID-19. We used this definition to call more attention to clinical screening and treatment among COVID-19 patients with newly diagnosed diabetes at hospital admission.

Conclusion

The present study found that hospitalized COVID-19 patients with newly diagnosed diabetes and known diabetes had an increased risk of all-cause mortality. COVID-19 patients with newly diagnosed diabetes had the highest risk of all-cause mortality compared with COVID-19 patients with known diabetes, hyperglycemia and normal glucose. Our study suggests that patients with COVID-19 need to be under surveillance for blood glucose screening, and COVID-19 patients with newly diagnosed diabetes should be paid more attention to the combination therapy for all COVID-19-related complications.

Figure legend

Figure 1. The Cumulative hazard of mortality according to different glucose categories among patients with COVID-19. Adjusted for age, sex, smoking, systolic blood pressure, and total cholesterol.

Figure 2. Hazard ratios for all-cause mortality based on different levels of fasting glucose among COVID-19 patients without known diabetes. Adjusted for age, sex, smoking, systolic blood pressure, and total cholesterol.

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Contributors

Huiqing Li, Shenghua Tian and Ting Chen drafted the manuscript. Juan Zheng, Huiqing Li, Tianshu Zeng, Lulu Chen, and Jiaoyue Zhang did literature research. Shenghua Tian, Zhenhai Cui, Ningjie Shi, Xueyu Zhong, Kangli Qiu, and Huiqing Li collected the epidemiological and clinical data. Ting Chen, Huiqing Li, and Ningjie Shi contributed to the statistical analysis. Ting Chen contributed to drawing tables in this manuscript. Juan Zheng, and Lulu Chen conceived and supervised the overall study. All authors reviewed and approved the final version of the manuscript. Huiqing Li, Shenghua Tian, and Ting Chen contributed equally to this study.

Ethical approval: The case series was approved by the ethics committee of Union hospital, Tongji Medical College, Huazhong University of Science and Technology (Ethical review No20200015). Written informed consent was waived owing to the rapid emergence of this infectious disease.

Declaration of interests

All authors declared no conflict of interest.

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Table 1. Baseline characteristics according to different glucose categories among patients with COVID-19

	Normal glucose	Hyperglycemia	Newly diagnosed diabetes	Known diabetes	P values
No. of participants	132	129	94	98	
Age, years	51.9 (1.20)	57.5 (1.20)	62.2 (1.42)	65.3 (1.38)	<0.001
Men, %	54 (40.9)	68 (52.7)	58 (61.7)	56 (57.1)	0.011
Body mass index, kg/m^2 *	23.0 (0.36)	24.5 (0.34)	24.4 (0.45)	25.3 (0.41)	<0.001
Systolic blood pressure, mmHg	130 (1.49)	132 (1.45)	131 (1.71)	135 (1.70)	0.081
Diastolic blood pressure, mmHg	80.7 (1.04)	81.3 (1.01)	81.1 (1.19)	82.2 (1.18)	0.825
Heart rate, times/minute	85.9 (3.69)	97.3 (3.59)	95.5 (4.25)	94.9 (4.23)	0.136
Past or current smoking, %	11 (8.3)	21 (16.3)	19 (20.2)	19 (19.4)	0.046
History of chronic diseases, %					
Diabetes	0 (0)	0 (0)	0 (0)	98 (100%)	-
Hypertension	25 (18.9)	33 (25.6)	39 (41.5)	53 (54.1)	<0.001
Coronary heart disease	11 (8.3)	9 (7.0)	8 (8.5)	16 (16.3)	0.092

Stroke	2 (1.5)	1 (0.8)	5 (5.3)	8 (8.2)	0.007
Chronic pulmonary disease	4 (3.0)	10 (7.8)	4 (4.3)	7 (7.1)	0.310
Chronic liver disease	1 (0.8)	3 (2.3)	6 (6.4)	2 (2.0)	0.096
Chronic kidney disease	1 (0.8)	2 (1.6)	2 (2.1)	3 (3.1)	0.649
Cancer	4 (3.0)	8 (6.2)	11 (11.8)	6 (6.2)	0.070
Signs and symptoms, %					
Fever	95 (72.0)	106 (82.2)	77 (81.9)	72 (73.5)	0.12
Cough	81 (61.4)	80 (62.0)	61(64.9)	52 (53.1)	0.36
Dyspnea	25 (18.9)	32 (24.8)	35 (37.2)	18 (18.4)	0.006
Sputum production	30 (22.7)	37 (28.7)	26 (27.7)	18 (18.4)	0.27
Haemoptysis	2 (1.5)	4 (3.1)	0 (0)	3 (3.1)	0.29
Fatigue	41 (31.1)	62 (48.1)	47 (50.0)	45 (45.9)	0.010
Headache	10 (7.6)	8 (6.2)	4 (4.3)	4 (4.1)	0.63
Nausea or vomiting	6 (4.5)	8 (6.2)	9 (9.6)	9 (9.2)	0.39
Diarrhoea	24 (18.2)	16 (12.4)	12 (12.8)	17 (17.3)	0.48

Muscle soreness, unit	29 (22.0)	36 (27.9)	28 (29.8)	28 (28.6)	0.53
Poor appetite	15 (11.4)	18 (14.0)	14 (14.9)	19 (19.4)	0.40
Chest distress	23 (17.4)	27 (20.9)	30 (31.9)	20 (20.4)	0.07
Palpitation	4 (3.0)	4 (3.1)	5 (5.3)	3 (3.1)	0.79
Chest pain	3 (2.3)	2 (1.6)	0 (0)	1 (1.0)	0.62
Rhinobyon	3 (2.3)	3 (2.3)	2 (2.1)	3 (3.1)	0.98
Pharyngalgia	6 (4.5)	4 (3.1)	1 (1.1)	1 (1.0)	0.33
Polypnea	19 (14.4)	26 (20.2)	19 (20.2)	20 (20.4)	0.55
Arthralgia	1 (0.8)	0 (0)	0 (0)	1 (1.0)	0.83
Dizziness	5 (3.8)	3 (2.3)	4 (4.3)	5 (5.1)	0.73
Onset of symptom to, days					
Hospital admission	15.8 (1.12)	17.1 (1.09)	13.9 (1.27)	16.3 (1.28)	0.29
Confirmation of COVID-19	9.1 (0.99)	10.3 (0.96)	9.9 (1.12)	10.4 (1.13)	0.81
Exposure history, %					
Exposure to Huanan seafood market	0 (0)	1 (0.8)	1 (1.1)	0 (0)	0.55

Exposure to infected cases	34 (25.8)	21 (16.3)	8 (8.5)	9 (9.2)	0.004

Data are means (SE) and are adjusted for age and sex unless otherwise indicated percentages. * Data were available for almost participants. Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; Hyperglycemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%; Newly diagnosed diabetes, fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%; Known diabetes, a history of diabetes.

Table 2. Laboratory measurements according to different glucose categories among patients with COVID-19

	Normal glucose	Hyperglycemia	Newly diagnosed diabetes	Known diabetes	P values
No. of participants	132	129	94	98	

White blood cell count,$\times 10^9$/L	5.82 (0.25)	5.92 (0.24)	6.97 (0.28)	6.81 (0.28)	0.003
Neutrophil count, $\times 10^9$/L	3.85 (1.10)	5.96 (1.07)	5.70 (1.26)	4.83 (1.25)	0.53
Lymphocyte count, $\times 10^9$/L	1.41 (0.07)	1.45 (0.07)	0.94 (0.08)	1.36 (0.08)	<0.001
Monocyte count, $\times 10^9$/L	0.45 (0.02)	0.43 (0.02)	0.35 (0.02)	0.45 (0.02)	0.001
Platelet count, $\times 10^9$/L	214 (7.46)	226 (7.24)	214 (8.57)	215 (8.49)	0.62
C-reactive protein, mg/L	18.3 (3.64)	24.4 (3.47)	52.2 (4.00)	36.6 (4.01)	<0.001
Erythrocyte sedimentation rate, mm/h	34.9 (3.10)	47.1 (3.11)	58.9 (3.82)	51.0 (3.99)	<0.001
Prothrombin time, s	13.4 (0.31)	13.0 (0.30)	14.1 (0.35)	13.3 (0.36)	0.094
Activation of partial thromboplastin time, s	41.4 (2.55)	37.1 (2.46)	41.6 (2.88)	39.1 (2.96)	0.56
D-Dimer >0.5 mg/L, %	44 (42.7)	36 (33.6)	39 (55.7)	40 (53.3)	0.011
Fibrinogen, g	3.57 (0.10)	3.90 (0.10)	4.17 (0.12)	4.18 (0.12)	<0.001
Thrombin time, s	17.0 (0.67)	15.6 (0.64)	16.3 (0.75)	15.9 (0.77)	0.49
Alanine aminotransferase, U/L	35.8 (3.30)	44.0 (3.19)	53.6 (3.77)	38.3 (3.75)	0.003
Aspartate aminotransferase, U/L	32.2 (2.78)	34.7 (2.69)	50.7 (3.18)	32.7 (3.16)	<0.001
Blood urea nitrogen, mmol/L	5.66 (0.42)	4.98 (0.40)	7.20 (0.47)	6.30 (0.47)	0.004

Creatinine, μmol/L	84.8 (7.00)	70.4 (6.80)	74.4 (8.03)	72.8 (7.99)	0.49
Lactate dehydrogenase	226 (12.9)	244 (12.5)	363 (14.6)	270 (14.5)	<0.001
Total bilirubin, μmol/L	11.8 (0.87)	10.9 (0.84)	13.5 (0.99)	11.5 (0.98)	0.22
Albumin, g/L	37.2 (1.67)	34.7 (1.61)	32.7 (1.91)	34.1 (1.90)	0.37
Total cholesterol, mmol/L	4.21 (0.12)	4.62 (0.12)	4.18 (0.14)	4.22 (0.14)	0.044
Triglyceride, mmol/L	1.39 (0.10)	1.58 (0.10)	1.66 (0.11)	1.72 (0.11)	0.148
High-density lipoprotein cholesterol, mmol/L	1.13 (0.04)	1.03 (0.04)	1.05 (0.04)	0.99 (0.04)	0.075
Low-density lipoprotein cholesterol, mmol/L	2.43 (0.10)	2.87 (0.10)	2.35 (0.11)	2.43 (0.11)	0.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	90.7 (12.5)	117 (12.1)	96.9 (14.3)	95.2 (14.2)	0.44
Cystatin C, mg/L	0.83 (0.48)	1.10 (0.46)	2.77 (0.55)	1.04 (0.55)	0.042
Fasting glucose, mmol/L	4.97 (0.18)	5.81 (0.18)	8.86 (0.21)	8.72 (0.21)	<0.001
Procalcitonin, ng/ml	0.23 (0.16)	0.17 (0.14)	0.51 (0.18)	0.32 (0.17)	0.49

Data are means (SE) and are adjusted for age and sex unless otherwise indicated percentages.

Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; Hyperglycemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%; Newly diagnosed diabetes,

fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%; Known diabetes, a history of diabetes.

Table 3. Treatments and outcomes according to different glucose categories among patients with COVID-19

	Normal glucose	Hyperglycemia	Newly diagnosed diabetes	Known diabetes	P values
No. of participants	132	129	94	98	
Treatments, %					
Antiviral therapy	114 (86.4)	117 (90.7)	84 (89.4)	80 (81.6)	0.203
Antibiotic therapy	87 (65.9)	88 (68.2)	75 (79.8)	70 (71.4)	0.132
Use of corticosteroid	26 (19.7)	38 (29.5)	44 (46.8)	36 (36.7)	<0.001

Intravenous immunoglobin	23 (17.4)	33 (25.6)	34 (36.2)	20 (20.4)	0.009
Oxygen support, %	94 (71.2)	102 (79.1)	84 (89.4)	90 (91.8)	<0.001
Nasal cannula	86 (65.2)	85 (65.9)	45 (47.9)	63 (64.3)	0.023
Mask	2 (1.5)	4 (3.1)	11 (11.7)	10 (10.2)	0.002
Non-invasive ventilation or high-flow nasal cannula	3 (2.3)	7 (5.4)	17 (18.1)	8 (8.2)	<0.001
Invasive mechanical ventilation	3 (2.3)	6 (4.7)	11 (11.7)	9 (9.2)	0.018
Antihypertensive medicines	28 (21.2)	42 (32.6)	39 (41.5)	40 (40.8)	0.003
Glucose-lowering medicines before hospital admission	0	0	0	60 (63.8)	-
Glucose-lowering medicines during hospital admission	1 (0.8)	4 (3.1)	23 (24.5)	68 (69.4)	<0.001

Lipid-lowering medicine	6 (4.5)	12 (9.3)	10 (10.6)	15 (15.3)	0.051
Illness severity, %					<0.001
Non-severe	51 (38.6)	36 (27.9)	10 (10.6)	17 (17.3)	<0.001
Severe or critical	81 (61.4)	93 (72.1)	84 (89.4)	81 (82.7)	<0.001
Complications, %					
Acute respiratory distress syndrome	1 (0.8)	4 (3.1)	10 (10.6)	3 (3.1)	0.001
Acute cardiac injury	27 (21.3)	26 (20.5)	23 (24.7)	32 (34.4)	0.079
Acute kidney injury	2 (1.5)	4 (3.1)	16 (17.0)	15 (15.3)	<0.001
Shock	3 (2.3)	6 (4.7)	22 (23.4)	11 (11.2)	0.005
Hypoalbuminemia (albumin <30g/L)	14 (10.8)	25 (19.4)	37 (39.4)	36 (36.7)	<0.001
Coagulopathy	12 (10.1)	12 (10.1)	15 (17.0)	17 (19.5)	0.070

Length of hospital stay, days	22.5 (1.19)	21.9 (1.16)	26.5 (1.37)	23.6 (1.37)	0.046
ICU admission, %	2 (1.5)	8 (6.2)	11 (11.7)	4 (4.1)	0.008
Prognosis, %					
Discharge, No	130 (98.5)	123 (95.3)	74 (78.7)	87 (88.8)	<0.001
Death, No	2 (1.5)	6 (4.7)	20 (21.3)	11 (11.2)	<0.001

Data are means (SE) and are adjusted for age and sex unless otherwise indicated percentages.

Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; Hyperglycemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%; Newly diagnosed diabetes, fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%; Known diabetes, a history of diabetes.

Table 4. Hazard ratios of mortality according to different glucose categories among patients with COVID-19

	Hazard ratios (95% confidence intervals)			
	Normal glucose	Hyperglycemia	Newly diagnosed diabetes	Known diabetes
No. of participants	132	129	94	98
No. of cases	2	6	20	11
Person-days	3790	3769	2872	2916
Multivariable-adjusted Model 1	1.00	2.84 (0.57-14.1)	9.43 (2.19-40.6)	4.57 (1.01-20.6)
Multivariable-adjusted Model 2	1.00	3.29 (0.65-16.6)	9.42 (2.18-40.7)	4.63 (1.02-21.0)
Multivariable-adjusted Model 3	1.00	3.27 (0.63-17.1)	7.21 (2.18-32.1)	6.06 (1.32-27.8)
Multivariable-adjusted Model 4	1.00	2.64 (0.50-14.0)	5.63 (1.22-26.0)	8.76 (1.78-43.2)

Model 1 adjusted for age, and sex; Model 2 adjusted for age, sex, smoking, systolic blood pressure, and total cholesterol; Model 3 adjusted for variable in model 2 and also using antihypertensive drugs, using lipid-lowering agents, admission to ICU, and using invasive mechanical ventilation; Model 4 adjusted for variable in model 3 and also for using glucose-lowering drugs before inpatients and during inpatients, and using corticosteroid.

Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; Hyperglycemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%; Newly diagnosed diabetes, fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%; Known diabetes, a history of diabetes.

Fig.1

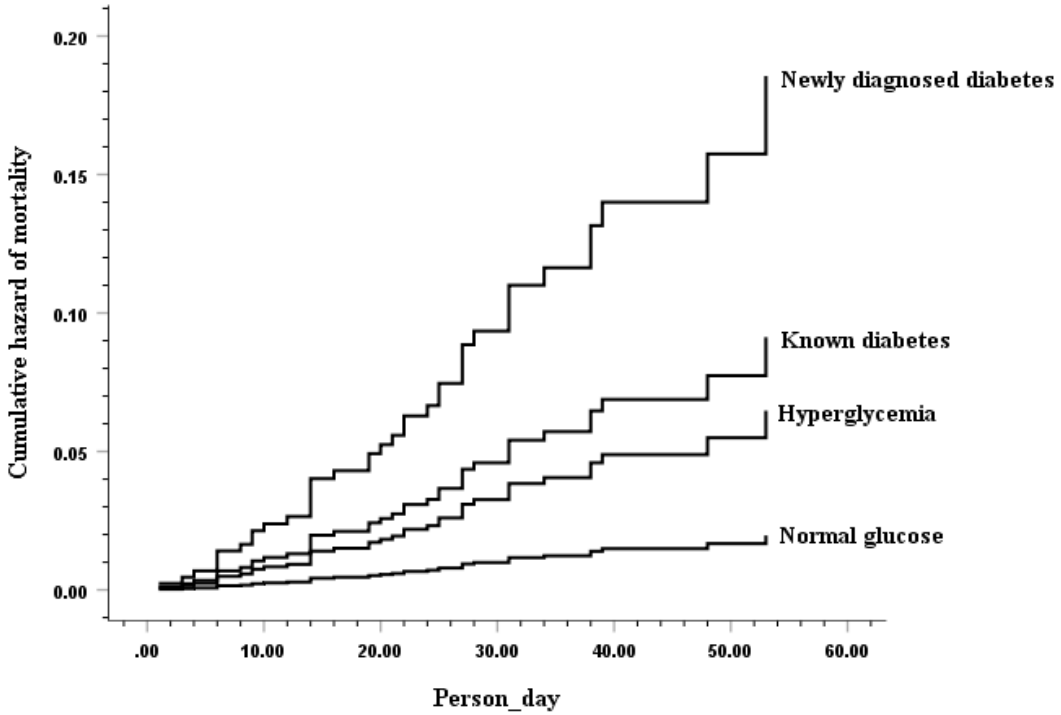

Fig.2